

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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In re Patent Application of:  
Maurizio Dalle CARBONARE et al.

Application No.: 10/019,387

Confirmation No.: 6340

Filed: March 26, 2003

Art Unit: 1612

For: USE OF HYALURONIC ACID DERIVATIVES  
FOR THE PREPARATION OF  
PHARMACEUTICAL COMPOSITIONS AND  
BIOMATERIALS FOR THE PREVENTION OF  
THE FORMATION AND URE OF  
CUTANEOUS SCARS

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Examiner: S. Maewall

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

I, Lanfranco Callegaro, do hereby declare the following:

1. Attached is a copy of my *curriculum vitae*.
2. I am working as the Chief Operating Officer of Fidia Farmaceutici, S.p.A. and I have worked in the field of biomedical research and protein chemistry since 1976.
3. I am an inventor in the above-referenced patent application, and am familiar with the development and properties of hyaluronic acid derivatives and their uses, in particular to reducing normotrophic scarring.
4. I have read and understand the subject matter of the Office Action of March 26, 2010.

5. The following experimental reports and comments are offered in support of the patentability of the instant invention.

6. I have attached as Attachment 1 the results of a study conducted to evaluate the effect of different Hyaluronic Acid formulations on wound healing. During the time the Experiments were conducted by Dr. Navsaria, I was the CEO and COO of Fidia Advanced Biopolymers S.r.L. (FaB). The report details experiments which were done with my knowledge and understanding, under the immediate direction of Dr. Alessandra Pavesio, (see page 2). The report details evidence as it was presented to me. I was actively involved in the design and in the discussion of results of the experiments reported in the report.

7. The following are my comments on the report in the context of the cited prior art, U.S. Patent 5,939,323 (hereinafter Valentini), Davidson et al., Clinical Materials (1991), and Dorigatti (WO 94/17837).

#### **8. Experimental Design**

The report by Dr. Navsaria details the method and results of an Experiment comparing the re-epithelialization of wounds in a pig model.

The Groups were as follows:

	Material Applied to Wound	Application Times
Group 1	Hyalofill-F™ (75% benzyl esterified derivative of HA) + Laserskin autograft (keratinocytes seeded onto a total benzyl ester of HA)	Hyalofill-F™ applied once, on the day of surgery Laserskin applied 7 days after surgery
Group 2	Hyalofill-F™ (75% benzyl esterified derivative of HA)	Hyalofill-F™ applied on day 0, 7, 14, 21, and 28
Group 3	Laserskin autograft (keratinocytes seeded onto a total benzyl ester of HA)	Laserskin applied 7 days after surgery
Group 4	-	-

The animals were given full thickness wounds and treated as above on day 0. All 4 groups were present on each animal. Animals were anesthetized on days 7, 14, 21, and 28, sites were treated, each wound was biopsied and photographed.

The results were measured by an image analysis of the photographs taken at each time point.

These photographs and the computer analysis led to a "percent reepithelialisation" end-point. The photographs were also used to assess the clinical appearance of the wounds at each time point.

The biopsy was either fixed and stained with Hematoxylin and eosin or Mallory trichromate, or snap frozen for immunohistochemistry analysis.

## **9. Results**

### **Percent Reepithelialization**

Approximately 70% of the wound is epithelialized in both Groups 1 and 2, both of which were the 75 % benzyl ester derivative of HA (Navsaria Report, page 8). In contrast, the group treated on day 7 with the graft of keratinocytes seeded onto a 100% benzyl ester of HA had only 27% reepithelialisation. Dr. Navsaria states that this result is significant ( $p<0.0001$ ). (Navsaria Report, page 8)

### **Clinical Appearance**

Dr. Navsaria indicates that "[T]here was more epidermal cover in wounds treated with Hyalofill (fig 3A and 3C) as compared to group 3 (fig 3b)." (Navsaria Report, page 8) Again, this demonstrates that the 75% benzyl ester derivative of HA performed better than the total benzyl ester of HA (seeded with keratinocytes).

### Histology

Dr. Navsaria indicates that the Hyalofill generates "a better organized wound bed . . . as compared to granulation tissue alone" at 1 week after surgery. (Navsaria Report, page 9) In addition, Dr. Navsaria states "[t]he most striking feature is the strong angiogenic response present in the wounds treated with Hyalofill and the blood vessels are perpendicular to the surface (directed angiogenesis)." (Navsaria Report, page 9).

Comparing the performance of the 75% benzyl ester of HA applied on day 0 (group 2) to the group treated with only the 100% benzyl ester of HA applied on day 7 (group 3), Dr. Navsaria states "[t]he collagen appears to be less mature compared with that in the Hyalofill treated wounds at equivalent time points." (Navsaria Report, page 9).

Similarly, comparing the performance of the 75% benzyl ester of HA applied on day 0 which also had the 100% benzyl ester of HA applied on day 7 (group 1) to the 75% benzyl ester of HA applied on day 0 (group 2), the addition of the 100% benzyl ester on day 7 did not appear to make a significant difference. Thus, the addition of the 100% benzyl ester of HA does not significantly increase the wound healing.

### 10. Commentary on Results

One of skill in the art would expect that a total benzyl ester of hyaluronic acid would be the best material for tissue implant/repair and wound healing because Campoccia teaches that a partial benzyl ester of hyaluronic acid produces side effects regarding cell proliferation, adhesion, and cell inflammation. Thus, I consider evidence that the partial benzyl ester is better at wound-healing would be unexpected in light of the Campoccia reference and the knowledge at the time.

This is supported by the results shown in the Navsaria report, which as discussed above, directly compares the total benzyl ester of hyaluronic acid to the 75% benzyl ester of hyaluronic acid in a wound healing model. In my opinion the results demonstrate that the application of a 75% benzyl ester of HA generates unexpectedly better wound epithelialisation, and demonstrate an

unexpectedly strong directed angiogenic response when compared to the 100% benzyl ester of HA.

In my opinion, these differences would have been unexpected at the time the above-referenced application was filed.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 09/26/2010

By   
Dr. Lanfranco Callegaro

Attachments: CV  
List of Publications  
Navsaria Report (Attachment 1)  
Campoccia